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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,207	10/09/2003	Winfried Linxweiler	MERCK-2289-D01	9231

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EXAMINER	
PAK, YONG D	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	**Application No.** 10/681,207	**Applicant(s)** LINXWEILER ET AL.	
	Examiner Yong D. Pak	**Art Unit** 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 08 September 2006.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 18-39 is/are pending in the application.

4a) Of the above claim(s) 27-39 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 18-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is 371 of PCT/EP00/00978, a divisional of 09/913,494.

The amendment filed on September 8, 2006, amending claim 18, has been entered.

Claims 18-39 are pending. Claims 27-39 are withdrawn. Claims 18-26 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on September 8, 2006, have been fully considered and are deemed to be persuasive to overcome some of the rejections/objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Sequence Compliance

This application is a contains sequence disclosure that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. To be in compliance, applicants are required to identify nucleotide sequences of at least 10 nucleotides and amino acid sequence of at least 4 amino acids in the specification by a proper sequence identifier, i.e. "SEQ ID NO:", see MPEP 2422.01).. It is particularly noted that the sequences in the specification, page 28 for example, lack sequence identification numbers. See particularly 37 CFR 1.821(d).

In response to the previous Office Action, applicants have traversed the above objection. Applicants argue that sequence identifier numbers are not necessary for page 28 since "a skilled worker can easily figure out the sequence from the totality of the disclosure" (Remarks, page 6). Examiner respectfully disagrees. Whether a skilled worker can easily figure out the sequence is immaterial. MPEP 2422 clearly states that "Patent applications which contain disclosures of nucleotide and/or amino acid sequences, in accordance with the definition in paragraph (a) of this section, shall, with regard to the manner in which the nucleotide and/or amino acid sequences are presented and described, conform exclusively to the requirements of §§ 1.821 through 1.825". According to § 1.821 through 1.825, applicants are required to identify nucleotide sequences of at least 10 nucleotides and amino acid sequence of at least 4 amino acids in the specification by a proper sequence identifier, i.e. "SEQ ID NO:", see MPEP 2422.01.

Hence the objection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 and claims 19-26 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the phrase "detecting presence of said linked glucose dehydrogenase, wherein said presence of glucose dehydrogenase correlates with gene expression of polypeptide X". It is not clear to the Examiner as to how those skilled in the art can conclude that polypeptide X is indeed expressed by detecting the "linked glucose dehydrogenase". This is because applicants have not set up any control steps to account for endogenous glucose dehydrogenases present in transformants comprising the fusion protein. The method does not recite any steps that would distinguish glucose dehydrogenase present in the fusion construct and the same glucose dehydrogenase endogenous to the transformants expressing the fusion construct. Therefore, the method lacks essential step(s).

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that requirement for reaction conditions such as control steps, etc. in the claims is contrary according to two cases, *Ex parte Jackson* & *Dinh-Nguyen* and well established PTO practice. Applicants also argue that the claimed methods can be practiced using a variety of reagents and/or steps without undue experimentation and limiting the claims to specific steps is not necessary. Examiner respectfully disagrees. MPEP 2172.01 states that "a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention". In this instant application, recitation of a control step is necessary in order to interrelate essential elements of the invention, correlation of presence of glucose dehydrogenase with expression of polypeptide X. Without it, it is not clear how those skilled in the art can conclude that polypeptide X is indeed expressed by detecting the “linked glucose dehydrogenase”. This is because the method does not recite any steps that would distinguish glucose dehydrogenase present in the fusion construct and the same glucose dehydrogenase endogenous to the transformants expressing the fusion construct.

Applicants also argue that the claims are definite because techniques assaying presence of enzymes are well known in the art. The rejection is not addressing whether the specification and art provides enough teachings in assaying for presence of glucose dehydrogenase, but if a skilled artisan can conclude that polypeptide X is indeed expressed by detecting the “linked glucose dehydrogenase”.

Applicants also argue that the rejected claim terms are common terms used in numerous patents issued by the PTO and a quick search can easily verify that the terms common in the art. Examiner respectfully disagrees. It is not clear to which terms applicants are referring to. As discussed above, the rejection is not addressing whether the specification and art provides enough teachings in assaying for presence of glucose dehydrogenase, but if a skilled artisan can not conclude that polypeptide X is indeed expressed by detecting the “linked glucose dehydrogenase”.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Current Protocols in Molecular Biology et al. in view of Yamada et al. and Yamanishi et al.

Claims 18-26 are drawn to a method for detecting expression of polypeptide X by expressing a gene encoding a recombinant fusion protein comprising glucose dehydrogenase linked with polypeptide X and detecting presence of said linked glucose dehydrogenase, wherein said presence of glucose dehydrogenase indicates expression of said polypeptide X.

Current Protocols in Molecular Biology (cited previously on form PTO-892) discloses that fusion proteins comprising a reporter protein and a protein of interest can be used to detect expression of the protein of interest by detecting the presence of the reporter protein (9.6) and a method of making fusion proteins (9.6). The reference also discloses a method of detecting a protein of interest by appending the protein with an eptitope tag and detecting antibodies that recognize said epitope (10.15) and detecting proteins by staining with a silver or coomassie blue stain (Chapter 10.2). With this teaching in hand, one having ordinary skill in the art would have concluded to use proteins well established in the art as the reporter protein, for ease of detecting its activity or its presence.

The difference between the reference of Current Protocols in Molecular Biology and the instant invention is that Current Protocols in Molecular Biology does not teach a method of detecting expression of polypeptide X by expressing a fusion protein comprising a glucose dehydrogenase as the reporter protein and detecting presence of said glucose dehydrogenase by wherein glucose dehydrogenase activity is detected using nitro blue tetrazolium or iodophenylnotrophenyl-phenyltetrazolium salt.

Glucose dehydrogenases are well known in the art. For example, Yamada et al. (form PTO-1449) discloses how to make a fusion protein comprising a heterologous protein and glucose dehydrogenase, wherein presence of the fused protein is analyzed by using an antibody against one of the proteins (page 12812). Even though Yamada et al. is not aimed at a method of detecting gene expression using glucose dehydrogenase as the reporter protein, Yamada et al. does teach a method of making a fusion protein comprising a glucose dehydrogenase and a heterologous polypeptide, which the skilled artisan can use to detect expression of one of the proteins by measuring the presence of the other protein in the fusion protein. Further, ExPASY (cited previously on form PTO-892) summarizes a list of known glucose dehydrogenases.

Also, detection of glucose dehydrogenase activity by assaying for its activity using a terazolium salt is well known in the art. Yamanishi et al. (US 4,622,296 – cited previously on form PTO-892) discloses a method of detecting glucose dehydrogenase by incubating a gel comprising the dehydrogenase with nitro blue tetrazolium or iodophenylnotrophenyl-phenyltetrazolium (Column 4).

Therefore, combining the teachings of Current Protocols in Molecular Biology Yamada et al. and Yamanishi et al., it would have been obvious to one having ordinary skill in the art to detect expression of a heterologous protein by expressing a fusion protein comprising the heterologous protein and a reporter protein, such as a glucose dehydrogenase, by detecting presence of the reporter by detecting antibodies raised against said reporter protein, assaying for activity of the reporter protein using tetrazolium salts and detecting presence of the reporter protein with a silver or coomassie blue stain. One of ordinary skill in the art would have been motivated to use glucose dehydrogenase as the reporter protein because the protein can be easily assayed. One of ordinary skill in the art would have had a reasonable expectation of success since Current Protocols in Molecular Biology teaches how to make fusion proteins and assaying for reporter protein activity, Yamada et al. teaches how to make a fusion protein comprising glucose dehydrogenase and a heterologous protein and Yamanishi et al. teaches how to measure activity of glucose dehydrogenase using tertrazolium salts.

Therefore, the above references render claims 18-26 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that one of ordinary skill in the art would not be able to reformulate the instant invention by merely combing the cited references nor be motivated to combine the cited reference because Current Protocoals in Molecular Biology describes a reporter system comprising a reporter gene fused with a promoter sequence of interest and assaying for the activity of a promoter using enzymatic or immunological detection and makes no reference to fusion proteins comprising a glucose dehydrogenase and a polypeptide of interest. Examiner respectfully disagrees. The cited reference discloses linking genes of interest to reporter genes and measuring the reporter gene product in order to determine expression of the gene of interest (9.6.3). With this teaching in hand, one having ordinary skill in the art would have concluded to use proteins well established in the art as the reporter protein, for ease of detecting its activity or its presence, such as a glucose dehydrogenase. Further, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). The reference of Current Protocoals in Molecular Biology. is relied on for its teaching of a fusion gene encoding a fusion protein comprising protein of interest and reporter protein, wherein the reporter protein can be assayed for determining the expression of the protein of interest. The rejection is based on the combined teachings of Current Protocols in Molecular Biology, Yamada et al. and Yamanishi et al. Upon combining the references, it would have been obvious to one having ordinary skill in the art to detect expression of a heterologous protein by expressing a fusion protein comprising the heterologous protein and a reporter protein, such as a glucose dehydrogenase, by detecting presence of the reporter by detecting antibodies raised against said reporter protein, assaying for activity of the reporter protein using tetrazolium salts and detecting presence of the reporter protein with a silver or coomassie blue stain. The motivation for combining the references is to use glucose dehydrogenase as the reporter protein since glucose dehydrogenases are well known in the art, assay for their activity is well known in the art and fusion proteins comprising glucose dehydrogenases are known in the art. One of ordinary skill in the art would have been able to reformulate the instant invention by combining the references because Current Protocols in Molecular Biology teaches how to make fusion proteins and assaying for reporter protein activity, Yamada et al. teaches how to make a fusion protein comprising glucose dehydrogenase and a heterologous protein and detecting expression of one of the proteins with antibodies against said protein and Yamanishi et al. teaches how to measure activity of glucose dehydrogenase using tertrazolium salts.

Applicants argue that one of ordinary skill in the art would not be able to reformulate the instant invention by merely combing the cited references nor be motivated to combine the cited reference because Yamada et al. does not describe a system or a method that encompasses the functional limitations of the instant invention. It appears that applicants that "functional limitations" is a method of detecting expression of a polypeptide of interest. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The reference of Yamada et al. is relied on for its teaching of a fusion protein comprising a heterologous protein and glucose dehydrogenase (page 12812). The rejection is based on the combined teachings of Current Protocols in Molecular Biology, Yamada et al. and Yamanishi et al. As discussed above, upon combining the references, it would have been obvious to one having ordinary skill in the art to detect expression of a heterologous protein by expressing a fusion protein comprising the heterologous protein and a reporter protein, such as a glucose dehydrogenase, by detecting presence of the reporter by detecting antibodies raised against said reporter protein, assaying for activity of the reporter protein using tetrazolium salts and detecting presence of the reporter protein with a silver or coomassie blue stain. The motivation for combining the references is to use glucose dehydrogenase as the reporter protein since glucose dehydrogenases are well known in the art, assay for their activity is well known in the art and fusion proteins comprising glucose dehydrogenases are known in the art. One of ordinary skill in the art would have been able to reformulate the instant invention by combining the references because Current Protocols in Molecular Biology teaches how to make fusion proteins and assaying for reporter protein activity, Yamada et al. teaches how to make a fusion protein comprising glucose dehydrogenase and a heterologous protein and detecting expression of one of the proteins with antibodies against said protein and Yamanishi et al. teaches how to measure activity of glucose dehydrogenase using tertrazolium salts.

Applicants argue that one of ordinary skill in the art would not be able to reformulate the instant invention by merely combing the cited references nor be motivated to combine the cited reference because Yamanishi et al. does not disclose fusion proteins in general or assay methods devoted to the measurement of the activity of fusion proteins comprising dehydrogenase and fails to mention glucose dehydrogenases fusion proteins. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The reference of Yamanishi et al. is relied on for its teaching of a method of detecting glucose dehydrogenase by incubating a gel comprising the dehydrogenase with nitro blue tetrazolium or iodophenylnotrophenyl-phenyltetrazolium (Column 4). As discussed above, the rejection is based on the combined teachings of Current Protocols in Molecular Biology, Yamada et al. and Yamanishi et al. As discussed above, upon combining the references, it would have been obvious to one having ordinary skill in the art to detect expression of a heterologous protein by expressing a fusion protein comprising the heterologous protein and a reporter protein, such as a glucose dehydrogenase, by detecting presence of the reporter by detecting antibodies raised against said reporter protein, assaying for activity of the reporter protein using tetrazolium salts and detecting presence of the reporter protein with a silver or coomassie blue stain. The motivation for combining the references is to use glucose dehydrogenase as the reporter protein since glucose dehydrogenases are well known in the art, assay for their activity is well known in the art and fusion proteins comprising glucose dehydrogenases are known in the art. One of ordinary skill in the art would have been able to reformulate the instant invention by combining the references because Current Protocols in Molecular Biology teaches how to make fusion proteins and assaying for reporter protein activity, Yamada et al. teaches how to make a fusion protein comprising glucose dehydrogenase and a heterologous protein and detecting expression of one of the proteins with antibodies against said protein and Yamanishi et al. teaches how to measure activity of glucose dehydrogenase using tertrazolium salts.

Hence the rejection is maintained.

None of the claims are allowable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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